REMARKS

Applicants have cancelled Claim 6 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 1 to remove reference to the Figure and to recite that the claimed antibody specifically binds to the polypeptide of SEQ ID NO: 78. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed June 23, 2004. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Priority Determination:

As an initial matter, the PTO issued the instant Office Action assuming that the earliest priority is the instant filing date, May 3, 2002. The PTO argued that the instant application and priority application Serial No. 10/006,867 do not meet the requirements of 35 U.S.C. § 112, first paragraph. However, for the reasons set forth below, the instant application and the priority application do meet the requirements of 35 U.S.C. § 112, first paragraph, and therefore, are entitled to an earlier priority date.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant "application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT

Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to U.S. Provisional Application 60/099741 filed 9/10/1998."

Applicants submit that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific utility. The sequences of SEQ ID NOs: 77 and 78 were first disclosed in US Provisional Application 60/099,741 filed 9/10/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-6 as lacking a specific, substantial, and credible utility. The PTO notes that the claims are drawn to antibodies which specifically bind to the polypeptide of SEQ ID NO:78. The PTO argues that the particular utilities asserted in the specification for the polypeptides and the nucleic acids encoding the peptides are not specific and substantial or well established. One of the asserted utilities for the polypeptides to which the claimed antibodies bind is use as a diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1357 cDNA is more highly expressed in normal stomach and lung as compared to stomach and lung tumor tissue, respectively. The PTO recognizes this as a "possible utility," however, the PTO asserts that there is no guidance on how to use this information, that no levels are disclosed, and that the information is too sparse to allow the encoding polynucleotide to be used as a diagnostic marker for stomach or lung tumor.

The PTO also argues that even if the polynucleotide has utility as a tumor marker, there is no such utility for the antibody binding to the encoded polypeptide because there is no reason to suspect that there is an alteration in the amount of the polypeptide in normal stomach and lung tissue compared to stomach and lung tumor tissue. The PTO asserts that it "is not known what the protein does or if the level of the protein of SEQ ID NO:78 in stomach or lung tumors corresponds to nucleic acid transcript level."

Applicants respectfully disagree and submit that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the Gene Encoding the PRO1357 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed antibodies. Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO1357 polypeptide in normal stomach and lung tissue compared to stomach and lung tumor tissue is insufficient because there is no guidance on how to use this information, no levels are disclosed, and because the information is too sparse to allow the encoding polynucleotide to be used as a diagnostic marker for stomach or lung tumor.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1).

With regard to the alleged sparseness or lack of guidance and information, including regarding the relative or absolute expression levels, Mr. Grimaldi explains in paragraphs 6 and 7, that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of

interest "can be used to differentiate tumor from normal." He explains that, "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO argues that "even if the polynucleotide had utility as a tumor marker, the antibody binding the encoded polypeptide has no such utility since there is no reason to suspect that there is alteration of the polypeptide sequence or amount in stomach or lung tumor *versus* normal tissue." Furthermore, the PTO argues that it is not known if "decreased gene amplification in tumors corresponds to a decrease in the amount of expressed protein."

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. The working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 2). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be

used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, Dr. Polakis and his colleagues have found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Additional references support this position. For example, Orntoft et al. (submitted herewith as Exhibit 4) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft et al.

showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman et al. (submitted herewith as Exhibit 5) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack et al. (submitted herewith as Exhibit 6) who studied a series of primary human breast tumors and found that "...62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (see column 1, abstract). Thus, these articles collectively teach that in general, there is a correlation between gene expression and mRNA expression.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of cases, the combined teachings in the art, exemplified by Orntoft et al., Hyman et al. and Pollack et al. and the Grimaldi and Polakis declarations, overwhelmingly teach that gene expression influences mRNA expression and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the gene expression data for the PRO1357 gene, that the PRO1357 protein is concomitantly over-expressed in normal lung cells as compared to lung tumor, and in normal stomach cells compared to stomach tumor cells. Thus, Applicants submit that the PRO1357 protein and the claimed antibodies have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules. Therefore, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed antibodies as a cancer diagnostic tool.

The Claimed Antibodies would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1357, which Applicants submit is not true, an antibody that binds to a

polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 7), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith (attached as Exhibit 8). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, an antibody that binds to a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed antibodies.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants assert that the above-discussed substantial utilities are specific to the claimed PRO1357 peptides.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1357 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene encoding the PRO1357 polypeptide is more highly expressed in normal stomach and lung tissue compared to stomach tumor and lung tumor tissue. These data are strong evidence that the PRO1357 polypeptide is associated with stomach and lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1357 polypeptide with a specific disease. This is a specific utility – it is not a general utility that would apply to the broad class of polypeptides and their antibodies.

Conclusion

The PTO has asserted two general arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO1357 gene is too sparse or lacking in information to be used as a cancer diagnostic; and, (2) that because there is no necessary correlation between gene amplification and protein expression, the claimed antibodies which bind the encoded polypeptides cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1357 gene in normal stomach and lung compared to stomach and lung tumor tissue, are real and significant. This declaration also indicates the data provide sufficient comparative and relative expression information and that given the relative difference in expression levels, the claimed antibodies which bind the encoded polypeptides have utility as cancer diagnostic tools.

Next, Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the claimed antibodies which bind the encoded polypeptides have utility as a diagnostic tool for cancer.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies that bind the PRO1357 polypeptides because PRO1357 is differentially expressed in certain cancer tissue compared to the corresponding normal tissue. This is not a general utility that would apply to the broad class of polypeptides.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies.

Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "specifically binds." The PTO argues that the phrase "specifically binds to" is defined in the specification at paragraph [0247] as binding to the target polypeptide "without substantial binding to any other polypeptide or polypeptide epitope." The PTO asserts that the term "substantial" makes the meets and bounds of the claims confusing. Thus, according to the PTO, it is not clear how binding of the antibody of Claim 1 and Claim 6 differ.

As set forth above, Claim 6 has been cancelled and Claim 1 has been amended to recite "specifically binds." Applicants submit that the term "specifically binds" has a well established meaning – for example, it refers to the binding of an antibody to a particular polypeptide, where the antibody does not substantially bind to any other polypeptide. One of skill in the art would readily understand the language of the claims to mean that the claimed antibodies bind to specifically defined polypeptides (in this case the polypeptides of SEQ ID NO: 78) but do not substantially bind to any other polypeptides. In view of the amendments to the claims, and since claim terms should be given their ordinary, art-recognized meaning, Applicants request reconsideration and withdrawal of the instant rejection.

Rejection under 35 U.S.C. §102(b) – Anticipation

Claims 1-6 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 01/16318 and WO 00/12708.

The cited references do not anticipate because the instant application claims priority to the cited references. Specifically, as set forth in the preliminary amendment filed on September 2, 2002, the instant "application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application **PCT/US00/23328** filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of

PCT Application **PCT/US99/20111** filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to U.S. Provisional Application 60/099741 filed 9/10/1998" (**emphasis added**). WO 01/16318 is the PCT publication of PCT/US00/23328, and WO 00/12708 is the PCT publication of PCT/US99/20111. Therefore, the cited PCT publications are improper references under § 102 and cannot anticipate the claimed subject matter.

The sequences of SEQ ID NOs: 77 and 78 were first disclosed in U.S. Provisional Application 60/099,741 filed 9/10/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the polypeptides to which the claimed antibodies bind, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

In view of the above discussion, reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

CONCLUSION

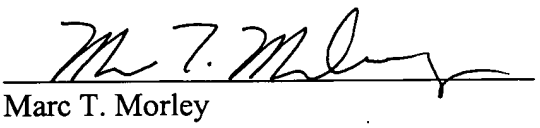
In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 9/22/04

By: 

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